This Page Is Inserted by IFW Operations and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents will not correct images, please do not report the images to the Image Problems Mailbox.

مر

number of animal models and in clinical trials by the present inventors. Also, plasmid DNA has been loaded into rat liver cells in vivo (Heller et al., FEBS Lett. 389, 225-28).

14

Page 2, the paragraph starting at line 21:

Protocols for the use of electroporation to load cells in vitro typically use a suspension of single cells or cells that are attached in a planar manner to a growth surface. In vivo electroporation is more complex because tissues are involved. Tissues are composed of individual cells that collectively make up a three-dimensional structure. In either case, the effects on the cell are the same. FIG 1 illustrates details of the electroporation procedure. Electrodes and electrode arrays for delivering electrical waveforms for therapeutic benefit, including inducing electroporation, have been described by Bernard (WO 98/47562).



Page 4, the paragraph starting at line 8:

3

Electropermeabilization of tumor cell membranes has been reported (Rols et al., Nature Biotechnology 16, 173, 1998) using applied electric pulses from surface electrodes in contact with the skin. Proteins and DNA can be transferred into the cells by incorporating either the protein or DNA carrying a reporter gene. The efficiencies of transfer for the protein and DNA were, respectively, 20% and 4%.

Page 8, the paragraph starting at line 18:

74

FIG. 4 is a bottom plan view of the embodiment of FIG. 3.

Page 12, the paragraph starting at line 7 To Pq12 Line 14



Each electrode 20 is in circuit communication with a respective portion of the source 1 of electrical energy. In a preferred embodiment this source comprises a pulse generator such as is known in the art (e.g., a PA-2000 or PA-4000, both from Cyto Pulse sciences, Inc., Columbia, MD; a T820, BTX, Inc., San Diego, CA) and adapted to deliver pulses of a predetermined shape, voltage, duration, and separation. In particular, the source 1 should be adapted to deliver voltage to each electrode 20 for establishing a first, low-

03/26/2002 18:19

level and a second, typically higher-level electromagnetic field in vivo between selected Selective control of the application of electrical signals between the individual electrodes can be accomplished in different ways, e.g., via the PA-201 Programmable Pulse Switch in combination with the PA-4000 generator (both from Cyto Pulse Sciences, Inc., Columbia, MD), or it can be done manually, mechanically, or electrically. Based on the particular need of the application of the system, the electrical energy may include, but are not limited to, rectangular direct current pulses, exponentially decreasing DC pulses, alternating current, exponentially increasing DC pulses, bipolar DC pulses, DC biased DC waveforms, DC biased AC waveforms, pulsed alternating current, and radio frequency waves. The system may also be controlled by a computer system with the appropriate software designed to enable selective control of the signal generator as defined by the electrode, target tissue, and/or specific treatment.

Page 16, the paragraph starting at line 15.

Details of the electrodes 68-71 in this embodiment will be presented for electrode 68, with the understanding that the other electrodes 69-71 have a similar configuration. (In FIG. 15, the electrode 69 is shown only partially to provide an inner view of electrode insulation 75.) Preferably the electrodes 68-71 comprise generally rectangular, clongated striplike members having insulation extending from the proximal end 84. This insulation electrically isolates each electrode member and can extend all the way from the proximal end 84 all the way to the distal end 80, leaving enough electrode surface exposed to allow energy transfer from the electrode members to the target tissue T. This insulation may be a separate member, a surface coating applied to the actual electrode member, or other type of insulation as known to those of skill in the art. At the distal end 80, the electrode 68 comprises a distal portion 80 that is electrically exposed at least on the side 82 facing the other electrodes to permit delivering a pulse therefrom. In a preferred embodiment the facing side 82 is substantially planar, although this geometry may be altered to suit a desired target tissue T. For example, in FIG. 12 is illustrated an alternate embodiment 100, wherein the electrodes 104-107 are curved to facilitate tissue contact. In addition, this embodiment shows the addition of barbs 108 to the distal ends 80 of the electrodes that serve as gripping means with respect to the target tissue T. These barbs are not



al

limited to use solely in this embodiment, it is understood that this feature may be incorporated into any of the electrodes disclosed herein.

Page 20, the paragraph starting at line 18. To Pg 20 Line 4

Further examples of tissue-contacting portions of the electrode structures are shown in FIGS. 22 and 23A-F. In these embodiments, the tissue contact member is able to be noncontiguous (FIG. 22) as opposed to the member shown in FIG. 9. Alternative geometries for the contact members are also within the scope of the invention (FIGS. 23A-F), and these can be square, rectangular, elliptical, triangular, kidney-shaped, free-form, or any other shape configured to the needs of the system as defined by the target tissue. The various electrode members may also have alternate shapes and sizes as shown by items 140-142. The shapes of the various electrodes are exemplary only and are not intended to be limited, but any shape is useable as available to one of ordinary skill in the art.

Page 21, the paragraph starting at line 18. To Page 1 Line 7

A second electrical potential is established between a pair of electrodes, which may or may not be the same poles on the multipolar electrode or pairs in the case of unitary polar members 20 and 21 as previously activated. The second potential is higher than the first electrical potential and is sufficient to cause electroporation in the target tissue T to enhance a movement of the desired molecule M into a cell. Exemplary field strengths and duration ranges include, but are not intended to be limited to, 1-10,000 V/cm in the nanosecond range to the millisecond range. In a particular embodiment the field strength range is 750-1500 V/cm over the microsecond to millisecond range. Either or both of the potentials can be delivered in a series of predetermined electrical pulses, each of which can comprise pulses delivered sequentially or simultaneously.

Page 23, the paragraph starting at line 10:

Another embodiment of a method of using one of the devices 10, 100, 110, or 120 comprises the step of introducing, such as by injection, although this is not intended as a limitation, a desired substance into the target tissue. The distal portions of the electrodes



68-72 are placed in contact with the tissue, and the sleeve 90, or the member 123 is moved to a position wherein the tissue area is encompassed by the electrodes 68-72, which ensures sufficient electrical contact therebetween. At least one, and preferably a plurality of, electrical pulses as desired are delivered to the electrodes 68-72 using the pulse generator 1, and thence to the tissue area for achieving electroporation and entrance of the desired substance into the target cells.

16 Page 24, the table beginning at line 21:

TABLE 1

Treatment Group	Number of Samples	Electrical Treatment	Mean Luciferase Expression
1	4	none	1,123,344
2	4	1500 V/cm 100 µs	1,735,343
3	4	1500 V/cm 100 µs, followed by 17 V/cm 100 ms	7,046,177
4	4	1500 V/cm 100 µs, followed by 40 V/cm, 20 ms	17,692,651

Exhibit A attached hereto indicates how the original paragraph was amended to produce the re-written paragraph submitted herewith. Added terms are underscored and deleted terms are bracketed. Assignee's executed Revocation of Power of Attorney and new Power of Attorney document is attached hereto.